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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/750,934
Filing Date: December 31, 2003
Appellant(s): TARARA ET AL.

Guy V. Tucker
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/25/2010 appealing from the Office action mailed 6/25/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 01/85136	WEERS	11-2001
US 2002/0037316	WEERS	3-2002
US 2002/0177562	WEICKERT	11-2002
WO 00/01365	DIDRIKSEN	1-2000

Weidmann, T.S. et al., "Drug Solubilization in Lung Surfactant," J. Controlled Release, vol 65 (1-2), 2000, p. 43-47.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weers *et al.* (WO 01/85136, whereby US 2002/0037316 is relied upon as equivalent), as evidenced by Weickert *et al.* (US 2002/0177562), Wiedmann *et al.* (*J. Controlled Release*, 2000, 65(1-2), p. 43-7), and Didriksen (WO 00/01365).

Weers discloses dry powder compositions of phospholipids which are efficiently delivered to the deep lung. The phospholipids may be administered alone or in combination with an active agent. The composition may be administered via a simple passive DPI device (paragraph 0011). The active agent may be ciprofloxacin (which inherently has the claimed solubility), amphotericin (i.e. which inherently has the claimed solubility), flunisolide (which inherently has the claimed solubility), etc. (paragraph 0022). Weers clearly teaches both soluble and insoluble actives (and dispersions thereof) in feedstock preparation. See paragraph 0022. See also paragraph 0062, wherein the active agent may also be dispersed directly in the emulsion, particularly in the case of water insoluble agents. Both water-insoluble (e.g. budenoside) and water soluble (e.g. nicotine bitratrate) drugs are exemplified (see Examples V or IX).

The medicament possess special physicochemical properties, such as high crystallinity (paragraph 0060), and include hollow porous aerodynamically light

microparticles with particle diameters appropriate for aerosol deposition into the lung (paragraph 0065 and 0048).

The medicament is formulated in a way such that it readily disperses into discrete particles with an MMD which is preferably from 0.5 – 5 μm (i.e. less than 10 μm, as claimed); a MMAD preferably from 1 – 4 μm (i.e. including less than about 2.6 μm, as claimed) (paragraph 0043). The powders typically have a bulk density less than 0.1 g/cm^3, or preferably less than 0.05 g/cm^3, as claimed (paragraph 0049). The geometric diameter is preferably less than 2.5 μm (i.e. which is less than 3 μm, as claimed) (paragraph 0070).

Phospholipids from both natural and synthetic sources are compatible with the present invention and may be used in varying concentrations to form the structural matrix. Exemplary phospholipids useful in the disclosed stabilized preparations include dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, etc. (paragraph 0032). Regarding claims 49-51, the particulate compositions may be used in conjunction with metered does inhalers, dry powder inhalers or nebulizers for liquid dose instillation techniques (paragraph 0042). Regarding claim 52, the powders can include a polyvalent cation (abstract). Regarding claim 53, the particles are made by spray-drying with a blowing agent (paragraph 0058). Regarding claim 41, it is noted that Weers does not specifically recite a fine particle fraction of his formulation. However, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. It is interpreted, absent

evidence to the contrary, that since Weers discloses particles of the same active agents (i.e. thus having the same solubility), and teaches that the particles are the same sizes (i.e. MMD, MMAD and geometric diameters) less than those is claimed, same bulk density, etc., and are made by the same methods as those claimed, the particles would inherently be capable of having the claimed inherent features such as fine particle fraction.

Regarding claim 104, with respect to the limitation that the active agent particles have a low Tg, comprising about 283 C, it is interpreted, absent evidence to the contrary, that the formulations of Weers would inherently meet this limitation because Weers teaches the same actives as those which are now claimed (e.g. amphotericin). Thus, the same active agent particles would inherently have the same Tg as that which is now claimed. This interpretation is supported by Applicants own specification, which recites that active agents have an inherent Tg (see published paragraph 0007 of specification). With regard to the limitation that the formulation is prepared by preparing a suspension of active agent particle and phospholipid and spray-drying, Weers also meets this limitation. See paragraph 0064, whereby the active agent may be solubilized (or dispersed) directly in the emulsion. In such cases, the active emulsion is simply spray dried without combining a separate active agent preparation. Furthermore, such a limitation appears to be a product-by-process type limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The instant claims require that the particulates do not comprise lactose. While it is noted that Example V demonstrates lactose, Weers clearly teaches that conventional DPIs comprise powdered formulations and devices where a predetermined dose of medicament, either alone or in a blend with lactose carrier particles, is delivered as an aerosol of dry powder for inhalation (paragraph 0042). Weers further teaches that by providing particles with very low bulk density, the minimum powder mass that can be filled into a unit dose container is reduced, which eliminates the need for carrier particles. That is, the relatively low density of the powders provides for the reproducible administration of relatively low dose pharmaceutical compounds. Moreover, the elimination of carrier particles will potentially minimize throat deposition and any "gag" effect, since the large lactose particles will impact the throat and upper airways due to their size (paragraph 0049).

Weers does not specifically recite the solubility of various active agents which may be used in the invention. It is for this reason that Weickert, Wiedmann and Didriksen are joined.

Weickert discloses that the aqueous solubility of amphotericin is 0.2 mg/ml (see Table 1).

Wiedmann discloses that the aqueous solubility of flunisolide is 1.2 μg/ml (i.e. 0.12 mg/ml) (see Abstract).

Didriksen discloses that ciprofloxacin has a solubility in water ranging from 0.1-0.3 mg/ml (see Abstract and page 8, lines 4-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a pharmaceutical formulation for pulmonary administration comprising porous particulates of amphotericin, ciprofloxacin, flunisolide, etc. in a matrix comprising a phospholipid having the claimed water solubility, geometric diameter, mass median diameter, bulk density, and mass median aerodynamic diameter, wherein the particulates do not comprise lactose. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Weers teaches that such active agents may be incorporated into such formulations with phospholipid for pulmonary administration (paragraph 0022). While Weers does not specifically recite the solubility of said active agents, Weers teaches that water soluble or water-insoluble agents may be incorporated into the formulations. Such active agents inherently have the claimed solubility, as evidenced by Weickert, Wiedmann or Didriksen. Regarding the presence of lactose in the formulation, Weers teaches that the relatively low density of the powders provides for the reproducible administration of relatively low dose pharmaceutical compounds. Moreover, the elimination of carrier particles will potentially minimize throat deposition and any "gag" effect, since the large lactose particles will impact the throat and upper airways due to their size (paragraph

0049), therefore one would have been motivated to eliminate lactose from the formulations since Weers teaches that elimination of lactose carrier particles.

Double Patenting

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68 and 103-105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/187,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to pharmaceutical formulations for pulmonary administration comprising particulates comprising an active agent particle wherein the active agent has a solubility in water of less than 1.0 mg/ml (amphotericin) in a lipid matrix, wherein at least 90% of the active agent particles in the pharmaceutical formulation have a geometric diameter less than 3 micrometers and wherein the particulates have a mass median diameter less than 20 micrometers. Accordingly, they are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(10) Response to Argument

Appellant's arguments have been fully considered but they are deemed unpersuasive. More specifically, Appellant argues on pages 6-8 of the Appeal Brief that independent claim 38 is drawn to a pharmaceutical formulation comprising

particulates comprising active agent particles in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. The active agent particles have a geometric diameter of less than about 3 micron and a solubility in water of about 0.1 to about 1.0 mg/ml. Appellants contend that Weers does not disclose particulates comprising active agent particles of the type claimed in a matrix comprising a phospholipid, wherein the particulates do not comprise lactose. Apellants assert that instead Weers discloses particulates where a solution of an active agent (as opposed to particles of active agent) is dispersed within a phospholipid matrix. The solution is spray-dried. Appellants argue that Example V is an exception to the above, in which budesonide particles are disclosed in a phospholipid matrix, however that in this example, the budesonide is combined with lactose, and that claim 38 excludes lactose-containing particles. Appellant argues that the lactose of Example V is not a carrier, but is a component of a solution that is used for suspending budesonide aprticles for spray-drying. Appellant argues that the Examiner's contention that it would have been obvious to remove lactose carrier particles is completely without moment since there are no lactose carrier particles in Example V. Appellant asserts that the Examiner has not accounted for lactose present in feedstock, and that it would not have been obvious to one of ordinary skill in the art to modify a single example of Weers in a manner that would arrive at Appellant's invention, particularly in the absence of any motivation to do so. Apellant argues that Weickert, Wiedmann and Didriksen could not be applied, with a reasonable likelihood of success, to Weers in a manner that would result in the invention of claim 38.

This is not found to be persuasive. Weers clearly teaches both soluble and insoluble actives, (and dispersions thereof) in feedstock preparation. See paragraph 0022. See also paragraph 0062: The active agent may also be *dispersed* directly in the emulsion, particularly in the case of water insoluble agents. As regards the presence of lactose as a carrier particle, in feedstock, one of ordinary skill in the art would recognize upon consideration of the Weers reference that "besides the aforementioned polymer materials and surfactants, it may be desirable to add other excipients to a particulate composition to improve particle rigidity, production yield, emitted dose and deposition, shelf-life, patient compliance, etc. Such *optional* excipients include coloring agents, taste-masking agents, buffers, hygroscopic agents, antioxidants, and chemical stabilizers. Further, various excipients may be incorporated in, or added to, the particulate matrix to provide structure and form to the particulate compositions. Listing of possible excipients includes lactose (paragraphs 0039-40). One of ordinary skill would have recognized that the presence of lactose in Example V is one of many possible excipients that may *optionally* be included in formulations within the scope of the teaching of Weers, and modification of the example such as omission of lactose would have been within the skill of the ordinary artisan. One would have had a reasonable expectation of success in doing so because Weers recites lactose and other excipients as optional, therefore one of ordinary skill would expect that their presence is not necessarily required for the formulation. To further elaborate, example VII of Weers even shows a budesonide/phospholipid dispersion and emulsion with perfluorooctyl ethane utilized as feedstock which does not include lactose (paragraph 0096-0099).

Weickert, Wiedmann and Didriksen are included to show that various active agents recited by Weers (amphotericin, flunisolide, ciprofloxacin) inherently have the claimed solubility.

With respect to independent claim 54, Appellant argues on pages 8-9 of the Appeal Brief that Weers does not disclose particulates comprising active agent particles in a matrix comprising a matrix comprising a phospholipid, wherein the particulates do not comprise lactose.

The examiner's response to arguments regarding presence of lactose in the formulation is applied as above.

With respect to independent claim 104, Appellant argues on pages 9-10 of the Appeal Brief that Weers does not disclose particulates comprising active agent particles in a matrix comprising a matrix comprising a phospholipid, wherein the particulates do not comprise lactose.

The examiner's response to arguments regarding presence of lactose in the formulation is applied as above.

With regard to the Double Patenting rejection, Appellant indicates on page 10 of the Appeal Brief that a terminal disclaimer will be filed as appropriate upon indication of otherwise allowable claims.

No terminal disclaimer has been received at this time, therefore the claims stand rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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